

Low rifampicin concentrations in tuberculosis patients with HIV infection

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Abstract

Introduction: The efficacy of tuberculosis (TB) treatment in Human Immunodeficiency Syndrome (HIV) co-infected patients may be compromised by genetic and pharmacokinetic variation in drug disposition. Rifampicin is a critical component of TB treatment. We investigated the influence of drug transporter gene polymorphisms on rifampicin concentrations in TB-HIV co-infected patients in Durban, South Africa.

Methodology: Rifampicin concentrations were measured 2.5 hours post-dose (approximated peak, $C_{2.5hr}$) in patients receiving either 450mg or 600mg rifampicin, randomized to either integrated or sequential antiretroviral treatment. Patients were genotyped for SLCO1B1 (rs4149032) polymorphisms. A mixed effects regression model was fitted to assess the influence of various factors on rifampicin concentrations. TB recurrence rates were also estimated.

Results: In 57 patients, median (IQR) $C_{2.5hr}$ was 3.6 (2.8-5.0) $\mu\text{g/mL}$. Polymorphism frequency in the SLCO1B1 (rs4149032) drug transporter gene was high (0.76) and was associated with low median rifampicin $C_{2.5hr}$, 3.7 (2.8-5.0) $\mu\text{g/mL}$ in the heterozygous and 3.4 (2.7-4.7) $\mu\text{g/mL}$ in the homozygous variant carriers. Concentrations were also low in males ($p < 0.0001$) and those with low haemoglobin ($p = 0.02$). Although reinfection could not be distinguished from reactivation for the 43 patients followed post trial, the incidence of TB recurrence was 7.1 per 100 person-years. Of the eight patients in whom TB recurred, seven had the polymorphism.

Conclusion: Approximated peak rifampicin concentrations were well below the recommended target range of 8 to 24 $\mu\text{g/mL}$ in this patient population with its high frequency of the SLCO1B1 (rs4149032) polymorphism. Increased rifampicin dosage may be warranted in African, HIV- TB co-infected patients.

Key words: drug interactions; pharmacogenetics; TB recurrence; co-infection.

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Introduction

In 2011 it was estimated that globally 8.7 million people were newly infected with TB [1]. Of these, 1.2 million were also co-infected with HIV and most of these patients resided in sub-Saharan Africa [1]. In co-infected patients, integrated treatment with anti-TB drugs and antiretrovirals has been shown to improve survival [2]. However, drug interactions, drug tolerability and sub-optimal tuberculosis drug bioavailability remain a concern [3]. In addition, the pharmacokinetics of anti-TB drugs are influenced by other factors including genetics and disease states such as those that compromise immunity [4-6].

Rifampicin is a critical and potent component of first-line, multi-drug TB therapy because of its early sterilizing activity against *Mycobacterium tuberculosis* in the intensive phase and sustained activity against

persistent bacilli throughout the continuation phase of TB treatment [7,8]. Metabolism is mainly hepatic, with up to 24% and 50% of drug excreted in the urine and bile unchanged respectively [9]. Rifampicin induces several cytochrome P450 enzymes [10] and hepatocellular uptake is mediated by an organic anion-transporter polypeptide 1B1 (OAT1B1) coded for by the gene SLCO1B1 [11]. Polymorphisms in this gene influence rifampicin pharmacokinetics significantly and are implicated in low rifampicin exposure [6,12]. Anti-TB activity and development of resistance are linked to rifampicin concentrations [13,14] and rifampicin peak concentrations of 8 to 24 $\mu\text{g/mL}$ are generally considered to be associated with optimal bactericidal killing and post antibiotic effect [15].

The purpose of this study was to assess rifampicin concentrations in TB-HIV co-infected patients and to

investigate the phenotypic and genotypic attributes that may influence these concentrations.

Methodology

In the ‘Starting Tuberculosis and Antiretroviral Therapy’ (START) trial (CAPRISA 001: NCT00091936) described previously, patients ($n = 58$) who had no prior history of TB, were randomized equally to receive integrated TB and HIV treatment ($n = 29$) or HIV treatment following the completion of TB treatment ($n = 29$) [16]. In both arms, ART comprised of once daily enteric-coated didanosine (400 mg for participants > 60 kg; 250 mg for participants < 60 kg), lamivudine 300mg and efavirenz 600mg, but if > 50 kg and on TB treatment, then efavirenz 800mg was prescribed. TB treatment was provided using fixed dose combination (FDC) TB drugs, usually for 6 months, in a directly observed therapy (DOT) program. In the intensive phase of TB treatment each FDC tablet contained: rifampicin 120mg / isoniazid 60mg / pyrazinamide 300mg / ethambutol 200mg. In the continuation phase of TB treatment FDCs comprised rifampicin 300mg / isoniazid 150mg or rifampicin 150mg / isoniazid 100mg. FDCs were dosed according to weight bands detailed in the TB control programme guidelines in effect at the time of the study. Accordingly, rifampicin dose was 450mg daily for five days a week in patients weighing < 50 kilograms (kg) or 600mg dosed daily five times a week in patients weighing 50 kg or more [16].

Blood samples were collected from 57 patients, at weeks 4, 8 and 12 of TB treatment at 2.5 hours post-dose in order to approximate peak rifampicin concentrations. Serum rifampicin concentrations were measured by tandem HPLC mass spectrometry using a methodology described previously [17]. The assay had a lower limit of quantitation of 0.1 $\mu\text{g/mL}$ and inter- and intra-day coefficients of variation below 10%. DNA for the genotyping of the drug transporter gene coded by *SLCO1B1* (rs4149032), previously shown to be associated with low rifampicin concentrations [12], was extracted from stored peripheral blood mononuclear cells using the Roche MagNA Pure LC DNA kit I (Version 17.0, Roche Diagnostics, Mannheim, Germany). Allelic discrimination reactions were performed in duplicate using a TaqMan (Applied Biosystems, Foster City, USA) commercial genotyping assay (C_1901709_10, rs4149032). Real Time polymerase chain reaction (RT-PCR) was performed on the Roche Light Cycler 480 platform (Roche Diagnostics, Mannheim, Germany). The final

volume for each reaction was 25 μL , consisting of TaqMan Genotyping Master Mix (Applied Biosystems, Foster City, CA, USA), 40X drug metabolising genotype assay mix and 10ng of genomic DNA. The thermal cycler conditions were as follows: initial step: 95°C for 10 minutes, then 50 cycles consisting of denature at 92°C for 15 seconds and anneal/extend at 60°C for 90 seconds.

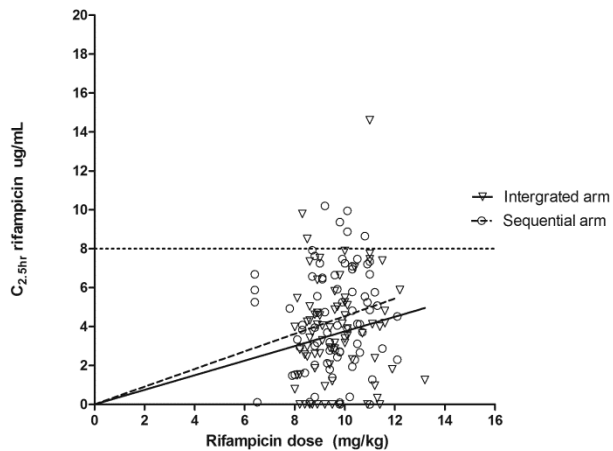
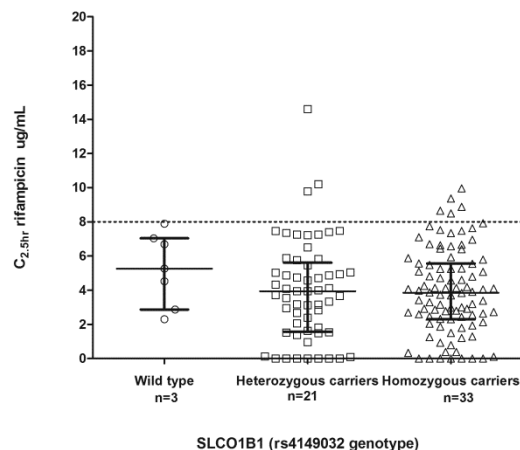
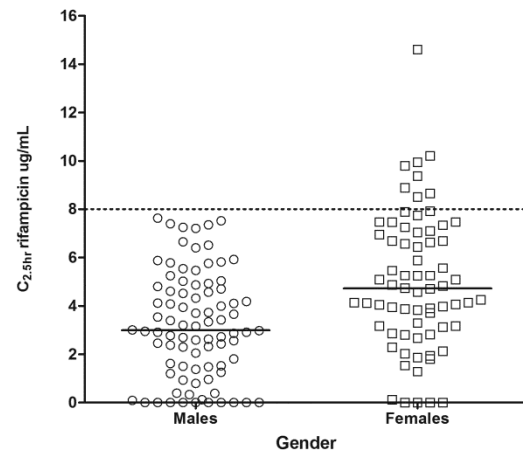
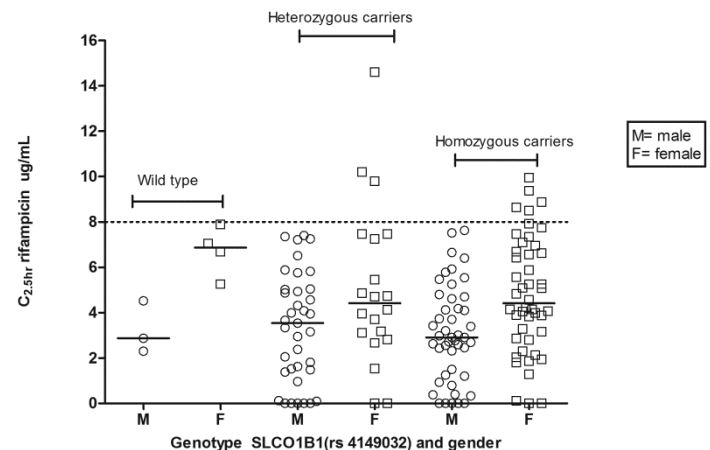
Data analysis was performed with SAS version 9.3 (SAS Institute Inc., Cary, NC). A Mann-Whitney test was used to compare median rifampicin concentrations. A mixed effects regression model, suitable for repeated measures, was used to test the influence of variables of interest on rifampicin concentrations. Post-trial TB recurrence was assessed by determining the period of risk for TB acquisition as the time in follow-up from the initial successful TB treatment completion date up to the re-treatment date or the last clinical contact date available. Poisson approximations were used to calculate confidence intervals for TB recurrence rates. *SLCO1B1* (rs4049032) mutations were tested and found to be in Hardy-Weinberg equilibrium. A type 1 error, $\alpha = 0.05$, was used to reject the null hypothesis.

Ethics approval was obtained from the University of KwaZulu-Natal biomedical research ethics committee (E116/04) and all patients provided written informed consent.

Results

The median age of the 57 patients in this analysis was 33 years (range: 19-54). All were Black African and 56% were men. At baseline, mean (SD) weight was 57.3 (9.0) kg, BMI was 21.8 (3.6) Kg/m^2 , CD4 count was 282 (153) cells/ mm^3 and haemoglobin was 10.3 (1.6) g/dL.

Median duration of TB treatment was 219 days (range: 181-291 days) and was similar in both the integrated and sequential arms. One hundred and fifty six rifampicin concentrations were available for analysis from the 57 patients. Of these, 44 patients contributed concentrations at three time points, 11 at two and two at one time point. Median (IQR) rifampicin concentrations were 3.6 (2.8-5.0) $\mu\text{g/mL}$ overall and 3.5 (2.8-4.7) $\mu\text{g/mL}$ and 3.7 (2.8-5.2) $\mu\text{g/mL}$ in the integrated and sequential treatment arms respectively ($p = 0.8$). Relevant concentrations for the 450mg and 600mg dose of rifampicin were 3.29 (1.25-5.25) $\mu\text{g/mL}$ and 4.06 (2.91-5.76) $\mu\text{g/mL}$, respectively ($p = 0.06$). Taking weight into account the rifampicin dosages ranged from 6.4mg/kg -13.2 mg/kg (Figure 1) and were similar in both arms.

Figure 1. Graph of approximated peak rifampicin concentrations in relation to dose (mg/kg) for the integrated and sequential arms.**Figure 3.** Graph of approximated peak rifampicin concentrations and SLCO1B1 (rs4149032) allele frequencies. The median and interquartile range are represented by the bar and whiskers.**Figure 2.** Graph of approximated peak rifampicin concentrations and gender. The median concentration is denoted by the bar.**Figure 4.** Graph of approximated peak rifampicin concentrations, SLCO1B1 (rs4149032) genotype and gender. The median concentration is denoted by the bar.**Table 1.** Mixed effect model estimating the influence of selected variables on $C_{2.5hr}$ rifampicin concentrations

Variables (N = 57)	Univariate Model			Multivariate model		
	β estimate	SE	P value	β estimate	SE	P value
Weight (kg)	0.01	0.02	0.84	0.01	0.02	0.56
Female vs. Male	1.78	0.39	<0.0001*	2.64	0.48	<0.0001*
Age (years)	-0.01	0.03	0.65	0.05	0.03	0.09
Non –Smoker vs. Smoker (status at baseline)	1.14	0.62	0.07	0.63	0.52	0.23
Dose/Weight (mg/kg)	0.09	0.16	0.56	0.33	0.16	0.04*
SLCO1B1 (rs4149032) allele						
Heterozygous vs. Wild type	-1.66	0.97	0.09	-1.45	0.83	0.09
Homozygous vs. Wild type	-1.63	0.93	0.09	-1.71	0.79	0.04*
Haemoglobin (g/dL)	-0.12	0.13	0.34	0.32	0.13	0.02*
CD4 Count (per 50 cell/mm ³ increase)	-0.04	0.07	0.59	0.019	0.07	0.76
TB recurrence vs. sustained cure	-0.10	0.67	0.88	0.10	0.56	0.86

*p<0.05, statistically significant

Women had a median rifampicin concentration of 4.1 (3.3-5.3) $\mu\text{g/mL}$ compared to 3.2 (2.6-4.1) $\mu\text{g/mL}$ in men ($p = 0.006$) as shown in Figure 2.

Allele frequency for *SLCO1B1* (rs4149032) polymorphism was 0.76. Fifty seven percent ($n = 33$) of patients were homozygous for the variant allele, while 38% ($n = 21$) were heterozygous and 5% ($n = 3$) were homozygous for the common allele of the gene (wild type). The median (IQR) rifampicin concentrations were 3.4 (2.7-4.7) $\mu\text{g/mL}$, 3.7 (2.8-5.0) $\mu\text{g/mL}$ and 5.3 (3.8-6.7) $\mu\text{g/mL}$ respectively (Figure 3). Figure 4 shows the relationship between rifampicin concentrations, genotype and gender.

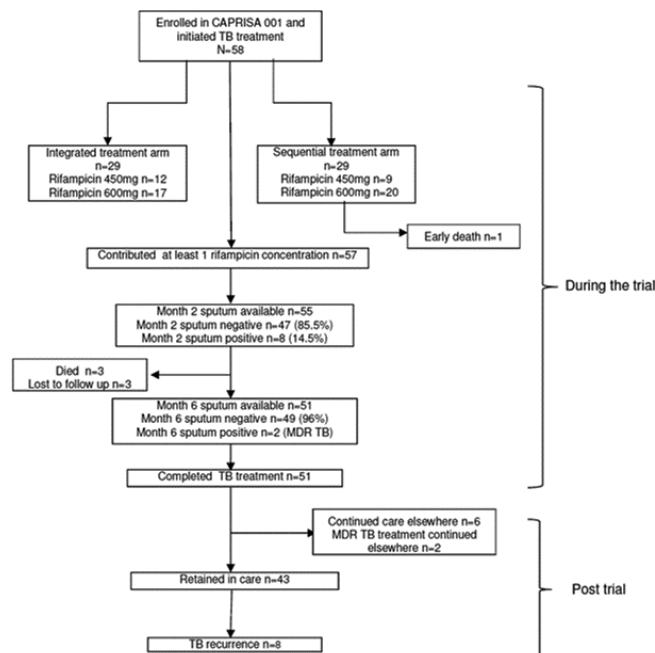
Predictors thought to influence rifampicin concentrations were tested in both univariate and multivariate models for repeated measures (Table 1). Male gender ($p < 0.0001$), haemoglobin per unit increase ($p = 0.02$) and homozygous variant allele carriers were associated with lower rifampicin concentrations. Higher dose per kilogram of body weight was associated with a higher rifampicin concentration ($p = 0.04$), but weight alone, smoking status, CD4 count and later TB recurrence were not predictive of lower rifampicin concentrations.

Patient outcomes, during and after the trial, are summarized in Figure 5. Sputum cultures were available at month two for only 55 of the 57 patients and 47 (85.4%) of these were found to be negative. Among the eight patients who were sputum positive, two had primary MDR TB and remained sputum positive throughout the study. Three subsequently developed recurrent TB, after completion of treatment, and the remaining three went on to become sputum negative at 6 months.

Fifty one of the 57 patients completed TB treatment and 49 of them were sputum culture negative at 6 months. The two with MDR TB who remained sputum positive are mentioned above. Of the 58 patients originally enrolled, four had died (one of unknown cause prior to contributing a drug level, one suicide, one embolism and one death was TB-related) and three had been lost to follow up.

Forty three patients continued receiving antiretroviral treatment at our CAPRISA clinic; eight (18.6%) of them developed recurrent TB during 113.1 person years of follow-up. The TB recurrence rate was 7.1 (95% CI: 3.1-13.9) cases per 100 person-years. The median time from completion of TB treatment to the post-trial diagnosis of recurrent TB was 639 days (range 56 – 1832 days). Of the eight patients in whom TB recurred, seven had the polymorphism and of these six were homozygous carriers of the variant allele.

Figure 5. Patient outcomes post enrollment.



TB treatment interruptions were investigated and durations of greater than 14 days occurred in two participants, both during the continuation phase of TB treatment. One patient, who was incarcerated and missed 19 days of treatment, was among the eight who had recurrent TB after treatment was completed. The other, the patient who died of TB, had missed a cumulative 43 days of treatment.

Discussion

The bactericidal activity of rifampicin is concentration dependent [18]. Ratios of both C_{\max} to MIC and AUC to MIC are important [5, 8], and a C_{\max} target range of 8 to 24 $\mu\text{g/mL}$ is recommended for optimal bactericidal activity and post-antibiotic effect [15]. Accordingly, the fact that our 57 patients had a median $C_{2.5\text{hr}}$ of 3.6 $\mu\text{g/mL}$, with none being $> 8 \mu\text{g/mL}$, is a cause for concern. As expected, median rifampicin concentrations were similar when HIV treatment was integrated or sequential.

Various factors could have contributed to our low rifampicin concentrations in both arms, one being the routine use of FDCs in South Africa, where formulation factors could affect bioavailability [19]. Consistent with the findings of earlier studies, male gender was associated with lower concentrations [20, 21] as was low haemoglobin, which has previously been linked to poorer TB outcomes [22]. HIV co-infection may also be a factor; in a group of 34 co-infected patients receiving 600mg of rifampicin daily,

where reported C_{\max} concentrations of $< 8\mu\text{g/ml}$ occurred in 77% of cases and 35% of these concentrations were $< 4\mu\text{g/ml}$. Overall the median was $5.4\mu\text{g/ml}$ [5]. Similarly, in 155 co-infected patients from Botswana, median C_{\max} values (at 2 hours) were 4.4 and $5.7\mu\text{g/ml}$ in those with CD4 counts of less than and greater than 200 cells/ μL respectively [23]. We found no association between CD4 count at baseline and rifampicin concentrations sampled.

We found the polymorphism frequency for the drug transporter gene SLCO1B1 (rs4149032) to be high in our patients (0.76) and mutations in this gene were associated with low rifampicin concentrations. Our allelic frequencies and related associations with low concentrations are very similar to those reported in Cape Town by Chigutsa *et al.* who found an allelic frequency of 0.70 and rifampicin $C_{\max} < 8\mu\text{g/ml}$ in 69% of their patients [12]. Evidence for the importance of the SLCO1B1 drug transporter gene in determining rifampicin exposure, also comes from a study by Weiner *et al.* These authors studied SLCO1B1 463C \rightarrow A and found that patients with this polymorphism had a 36% decrease in AUC₀₋₂₄. Their African patients had the highest frequency of this polymorphism [15] in contrast to the Cape Town study where the 463C \rightarrow A polymorphism was infrequent and did not appear to be associated with rs4149032 [12].

Limitations of the current analysis include the small sample size and the inability to assess for delayed absorption due to the single time point sampling, although from the literature, sampling 2-3 hours post administration is generally when peak rifampicin concentrations are reached. Moreover, in more than one occasion the same patient was sampled.

We were also unable to distinguish between reinfection and reactivation, as this was not part of the study design. However, TB recurred in 18.6% of patients who had been confirmed sputum negative at the end of TB treatment. Our recurrence rate of 7.1 per 100 person-years was comparable with the figure of 8.4 per 100 person-years in similar patients in a Ugandan study [24], although rifampicin concentrations were not measured in that study. While it was not possible to directly attribute recurrence in our study to low rifampicin concentrations, lower TB drug concentrations have previously been postulated to be associated with poorer treatment outcomes [8,15,23]. Of the 8 patients in whom TB recurred after treatment was completed, 87.5% had the polymorphism and 75% were homozygous for the variant allele. Furthermore, the TB related death was also in a patient homozygous for the variant allele in

whom low rifampicin concentrations had been measured. The two cases of MDR TB were primary and only diagnosed retrospectively and hence were unrelated to treatment and rifampicin concentrations.

Chigutsa *et al.*, who considered the SLCO1B1 (rs4149032) polymorphism an important determinant of the low rifampicin concentrations in African patients, recommended an increase to the current standard daily dose. After model simulations, they demonstrated that a daily dose increment of 150mg would produce concentrations similar to those achieved in wild type individuals and would reduce the percentage of patients with concentrations below $< 8\mu\text{g/ml}$ by 50% [12]. In support of a dose increase is a recent 14 day study where rifampicin doses of 10, 20, 25 and 30mg/kg produced mean C_{\max} concentrations of 7.4, 21.6, 25.1 and 33.1 mg/L in adult smear positive TB patients [25]. Evidence from this trial suggested that higher doses of rifampicin, even up to 35mg/kg, appear to be well tolerated, safe and exhibit optimal drug exposure [25].

Conclusion

Our patient cohort of TB-HIV co-infected Black South African patients exhibited both extremely low rifampicin concentrations and a high frequency of polymorphisms in the SLCO1B1 (rs4149032) drug transporter gene. Further research on the possible need for increased rifampicin dosage and a more comprehensive exploration of the role of polymorphisms in the SLCO1B1 drug transporter gene is warranted.

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